Check for updates

Updated guidelines for the management of dyslipidemia and the prevention of cardiovascular disease in adults by pharmacists

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Introduction

Cardiovascular disease (CVD) is the second leading cause of death in Canada.[1] The prevalence of ischemic heart disease continues to rise, highlighting the importance of effective long-term risk factor management.[2] Pharmacist-led dyslipidemia management has been demonstrated to lead to significant improvements in patient outcomes.[3-5] In this article, we provide guidelines on the management of dyslipidemia that are tailored to pharmacists, based on the 2021 Canadian Cardiovascular Society (CCS) Dyslipidemia Guidelines.[6] Notable updates in the new CCS guidelines since the 2016 version are highlighted in Table 1.

Who should be screened?

The CCS dyslipidemia guidelines continue to recommend screening all individuals 40 years of age or older as well as all individuals with 1 or more risk factors, as listed in Table 2. Further emphasis is given to screening of women who have had pregnancy complications. In addition to women with hypertensive disorders of pregnancy, the new CCS dyslipidemia guidelines have expanded their recommendation to include screening all women with a history of gestational diabetes, preterm birth, stillbirth, low-birth-weight infant or placental abruption. These pregnancy complications have been associated with a higher risk of developing cardiovascular risk factors, in addition to atherosclerotic CVD (ASCVD).[7,8]

How should patients be screened?

General screening

The CCS dyslipidemia guidelines continue to recommend the screening tests highlighted in Table 2. As per the previous guidelines, a lipid panel is recommended to be done in the nonfasting state unless the patient has a triglyceride (TG) level >4.5 mmol/L. Notable updates in the new guidelines are the roles of lipoprotein(a) (Lp[a]), non–high-density lipoprotein cholesterol (non–HDL-C), and apolipoprotein B (ApoB), as described below.

Role of Lp(a)

A notable update in the new CCS guidelines is the recommendation to measure Lp(a) once in a person's lifetime as part of initial lipid screening. Lp(a) is an LDL-like particle in which ApoB is covalently bound to a plasminogen-like molecule called apolipoprotein(a). It is genetically determined, so it is generally stable throughout an individual's life and is not influenced by age, sex, fasting state, inflammation, or lifestyle factors. Studies have demonstrated that high levels of Lp(a) have been associated with an increase in cardiovascular risk.[9-12] For patients with an elevated Lp(a) of ≥50 mg/dL, earlier and more intensive management of cardiovascular risk factors is recommended. Lp(a) does not yet have a treatment target or threshold, as there is currently established lack of quality evidence demonstrating a cardiovascular benefit with a reduction in Lp(a), which is another justification of why repeated measurements of Lp(a) are not currently indicated.

Role of non–HDL-C and ApoB

Further emphasis is given in the new guidelines to the roles of non–HDL-C and ApoB in the screening and monitoring of patients. These 2 lipid parameters are now generally preferred over LDL-C when interpreting lipid results because they provide a more accurate assessment of the total concentration of atherogenic particles compared with LDL-C. This has translated to a superior cardiovascular risk prediction when compared

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SUMMARY

- New evidence in the management of dyslipidemia has recently led to the publication of the 2021 Canadian Cardiovascular Society (CCS) dyslipidemia guidelines.
- This focused practice guideline update is tailored to pharmacists, based on the specific recommendations from the 2021 CCS dyslipidemia guidelines.
- This practice guideline update outlines the new recommendations and provides tips on implementation, including which patients to screen, how to perform cardiovascular risk assessment, and how to intensify therapy beyond statin treatment.
- With the known value of pharmacist-led dyslipidemia management, these proposed practice guidelines will assist pharmacists in practising to their full scope of practice and taking an active role in the management of patients with dyslipidemia.

RÉSUMÉ

- De nouvelles données sur la prise en charge de la dyslipidémie ont récemment mené à la publication des lignes directrices 2021 de la Société canadienne de cardiologie (SCC) sur la dyslipidémie.
- Cette mise à jour des lignes directrices axées sur la pratique est adaptée aux pharmaciens, et fondée sur les recommandations spécifiques des lignes directrices 2021 de la SCC sur la dyslipidémie.
- Cette mise à jour des lignes directrices axées sur la pratique décrit les nouvelles recommandations et fournit des conseils sur leur mise en œuvre, y compris sur les patients qui doivent se soumettre à un dépistage, sur la manière d'évaluer le risque cardiovasculaire et sur la façon d'intensifier le traitement autre que le traitement par statine.
- Compte tenu de la valeur reconnue de la prise en charge de la dyslipidémie par les pharmaciens, cette proposition de lignes directrices axées sur la pratique aidera les pharmaciens à exercer pleinement leur profession et à jouer un rôle actif dans la prise en charge des patients atteints de dyslipidémie.

with LDL-C.[13,14] The new guidelines also recommend using non–HDL-C and ApoB over LDL-C in patients with a TG level >1.5 mmol/L. Above this TG value, some cholesterol in LDL particles is replaced by TG, which promotes production of more atherogenic small dense LDL particles and makes the amount of cholesterol in LDL an unreliable reflection of LDL particle number.[6] Notably, the new guidelines include slightly modified non–HDL-C and ApoB parameters compared with the 2016 CCS guidelines to more accurately represent the same population percentile equivalents as LDL-C.

Who should receive therapy?

Statins remain the recommended first-line therapy for all patients with dyslipidemia.[6] To determine who to treat, pharmacists first need to assess a patient's cardiovascular risk. Patient risk may be divided into 2 categories: primary cardiovascular prevention (Figure 1) and those with statin-indicated conditions, which automatically confer a higher risk of CVD (Figure 2). For primary prevention patients, pharmacists should estimate a patient's long-term cardiovascular risk using a validated risk calculator (e.g., Framingham Risk Score: https://ccs.ca/app/uploads/2020/12/FRS_eng_2017_fnl1.pdf). Statin therapy is then recommended based on the patient's cardiovascular risk score (low, intermediate, or high) and baseline lipid levels. For all patients who already have a statin-indicated condition, statin therapy should be recommended, as they have demonstrated the largest absolute benefit in reducing cardiovascular events in these group of patients.

Assess cardiovascular risk

1. Statin-indicated conditions (patients are automatically considered to be at high cardiovascular risk):
   a. LDL-C ≥5 mmol/L, ApoB ≥1.45 g/L, or non–HDL-C ≥5.8 mmol/L or documented familial hypercholesterolemia
   b. Most patients with diabetes mellitus:
      i. ≥40 years of age, or
      ii. ≥30 years of age with ≥15 years' duration, or
      iii. presence of microvascular complications
   c. Chronic kidney disease (CKD) not treated with chronic dialysis, defined as age ≥50 years and estimated glomerular filtration rate <60 mL/min/1.73 m^2 or albumin-to-creatinine ratio >3 mg/mmol
   d. Patients with ASCVD (this refers to all clinical conditions of atherosclerotic origin):
      i. Coronary artery disease:
         - Acute coronary syndrome (ACS)
         - History of coronary artery bypass graft surgery or coronary stenting
         - Stable or unstable angina
         - Documented coronary artery disease by angiography
      ii. Cerebrovascular disease:
         - Stroke
         - Transient ischemic attack
         - Documented carotid disease
      iii. Peripheral artery disease:
         - Claudication and/or ankle-brachial index <0.9
         - Femoral popliteal bypass graft surgery

TABLE 1 Summary of changes in the 2021 CCS guidelines[6]

Screening and cardiovascular risk assessment	Therapy intensification
• All women with a history of gestational diabetes, preterm birth, stillbirth, low-birth-weight infant or placental abruption, in addition to hypertensive disorder of pregnancy, should be screened with a complete lipid panel in the late postpartum period. • Lipoprotein(a) level should be measured once in a person's lifetime as part of initial screening. • Non–high-density lipoprotein cholesterol and apolipoprotein-B levels are now generally preferred over low-density lipoprotein cholesterol in screening and monitoring.	• While initial therapy with a maximally tolerated statin is endorsed for all patients in whom therapy is recommended, intensification of therapy is suggested when a patient's lipid levels are above a defined threshold, as opposed to targeting a specific lipid level. • Based on new evidence for cardiovascular risk reduction, consider, in defined circumstances, the use of proprotein convertase subtilisin/kexin 9 (PCSK9 inhibitors) and icosapent ethyl. • Avoid recommending omega-3 polyunsaturated fatty acids for cardiovascular risk reduction, as there is contemporary evidence demonstrating that these supplements do not reduce cardiovascular risk.

TABLE 2 Summary of whom to screen and how to screen[6]

Whom to screen for dyslipidemia	How to screen for dyslipidemia

• Men 40 years of age or older; women 40 years of age or older (or postmenopausal)
  ○ Consider earlier screening in ethnic groups at increased cardiovascular risk, such as South Asian or Indigenous individuals
• All patients with any of the following conditions, regardless of age:
  ○ Clinical evidence of atherosclerosis
  ○ Abdominal aortic aneurysm
  ○ Diabetes mellitus
  ○ Arterial hypertension
  ○ Current cigarette smoking
  ○ Stigmata of dyslipidemia (corneal arcus, xanthelasma, xanthoma)
  ○ Family history of premature CVD†
  ○ Family history of dyslipidemia
  ○ CKD (estimated glomerular filtration rate, eGFR, ≤60 mL/min/1.73 m^2 or ACR ≥3 mg/mmol)
  ○ Obesity (BMI ≥30 kg/m^2)
  ○ Inflammatory diseases (RA, SLE, PsA, AS, IBD)
  ○ HIV infection
  ○ Erectile dysfunction
  ○ COPD
  ○ All women with history of pregnancy complications: hypertensive disorder of pregnancy, gestational diabetes, preterm birth, stillbirth, low-birth-weight infant, or placental abruption
	• For all:
	  ○ History and physical examination
	  ○ Standard lipid profile: total cholesterol, LDL-C,* HDL-C, non–HDL-C and TG
	  ○ Fasting plasma glucose or glycated hemoglobin
	  ○ eGFR
	  ○ Lp(a) once in a patient's lifetime, with initial screening
	• Optional
	  ○ ApoB
	  ○ Urine ACR (if the patient has an eGFR <60 mL/min/1.73 m^2, hypertension or diabetes)

ACR, albumin-to-creatinine ratio; ApoB, apolipoprotein-B; AS, ankylosing spondylitis; BMI, body mass index; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate; HDL-C, high-density lipoprotein cholesterol; HIV, human immunodeficiency virus; IBD, inflammatory bowel disease; LDL-C, low-density lipoprotein cholesterol; Lp(a), lipoprotein(a); PsA, psoriatic arthritis; RA, rheumatoid arthritis; SLE, systemic lupus erythematous; TG, triglycerides.

*Non–HDL-C or ApoB levels are preferable over LDL-C when interpreting lipid results, particularly when TG are ≥1.5 mmol/L.

†Men younger than 55 years of age and women younger than 65 years of age in first-degree relatives.

iv. Abdominal aortic aneurysm (atherosclerosis is a known culprit):
- Abdominal aorta >3.0 cm
- Previous aortic aneurysm surgery

2. Primary prevention patients (need to determine the patient's baseline cardiovascular risk):
   a. Cardiovascular risk can be assessed using the following validated scores:
      i. The modified Framingham 10-year Risk Score (FRS), available in the CCS guideline app
      ii. "Cardiovascular age" using the Cardiovascular Life Expectancy Model (online calculator available in the CCS guideline app or at http://myhealthcheckup.com/cvd/?lang=e)
      iii. For women with hypertensive disorders of pregnancy, the guidelines recommend favouring cardiovascular age over 10-year risk calculators
   b. Coronary artery calcium (CAC) score:
      i. CAC score testing involves a computed tomography scan of the chest to quantify calcification of the coronary arteries, which is a marker of atherosclerotic plaque.
      ii. Some intermediate-risk patients and subset of low-risk patients may undergo CAC screening.
      iii. CAC measurement >0 Agatston units (AU) confirms the presence of atherosclerotic plaque. A score >100 AU indicates significant coronary plaque burden and is considered to be a statin-indicated condition. Pharmacists can play an active role in identifying these patients to help initiate statin therapy.

Initiate statin therapy according to cardiovascular risk

1. Once cardiovascular risk assessment is complete, pharmacists should use the results to engage with their patient in a shared decision-making process. This includes:
   a. Ensuring that the patient understands their baseline cardiovascular risk
   b. Discussing the benefits that statins may offer in terms of cardiovascular risk reduction and their possible adverse effects
   c. Addressing any misconceptions that the patient may have about their cardiovascular risk and therapeutic options
2. Recommend initiating statin therapy according to the guidelines:
   a. Primary prevention patients (Figure 1):
      i. High-cardiovascular-risk patients (10-year FRS ≥20%): statin therapy recommended in *all* patients
      ii. Intermediate-cardiovascular-risk patients (10-year FRS of 10%-19.9%): recommend statin therapy if
- LDL-C ≥3.5 mmol/L, or non–HDL-C ≥4.2 mmol/L, or ApoB ≥1.05 g/L or
  - Other groups include patients fulfilling the HOPE-3 trial[15] criteria or patients who present with specific risk modifiers (*new recommendation in the guidelines*), as detailed in Figure 1

      iii. Low-cardiovascular-risk patients (10-year FRS of <10%): statin therapy generally not recommended for most low-risk individuals; however, exceptions for low-risk patient groups who may benefit from statin therapy are detailed in Figure 1
   b. Patients with statin-indicated conditions (Figure 2): statin therapy recommended in *all* patients.
3. Treatment in older adults:
   a. Emerging evidence continues to demonstrate that there are benefits to maintaining low levels of atherogenic lipoproteins at any age. This includes the benefits of lipid-lowering therapy for primary prevention patients who are ≥75 years of age.[16,17]

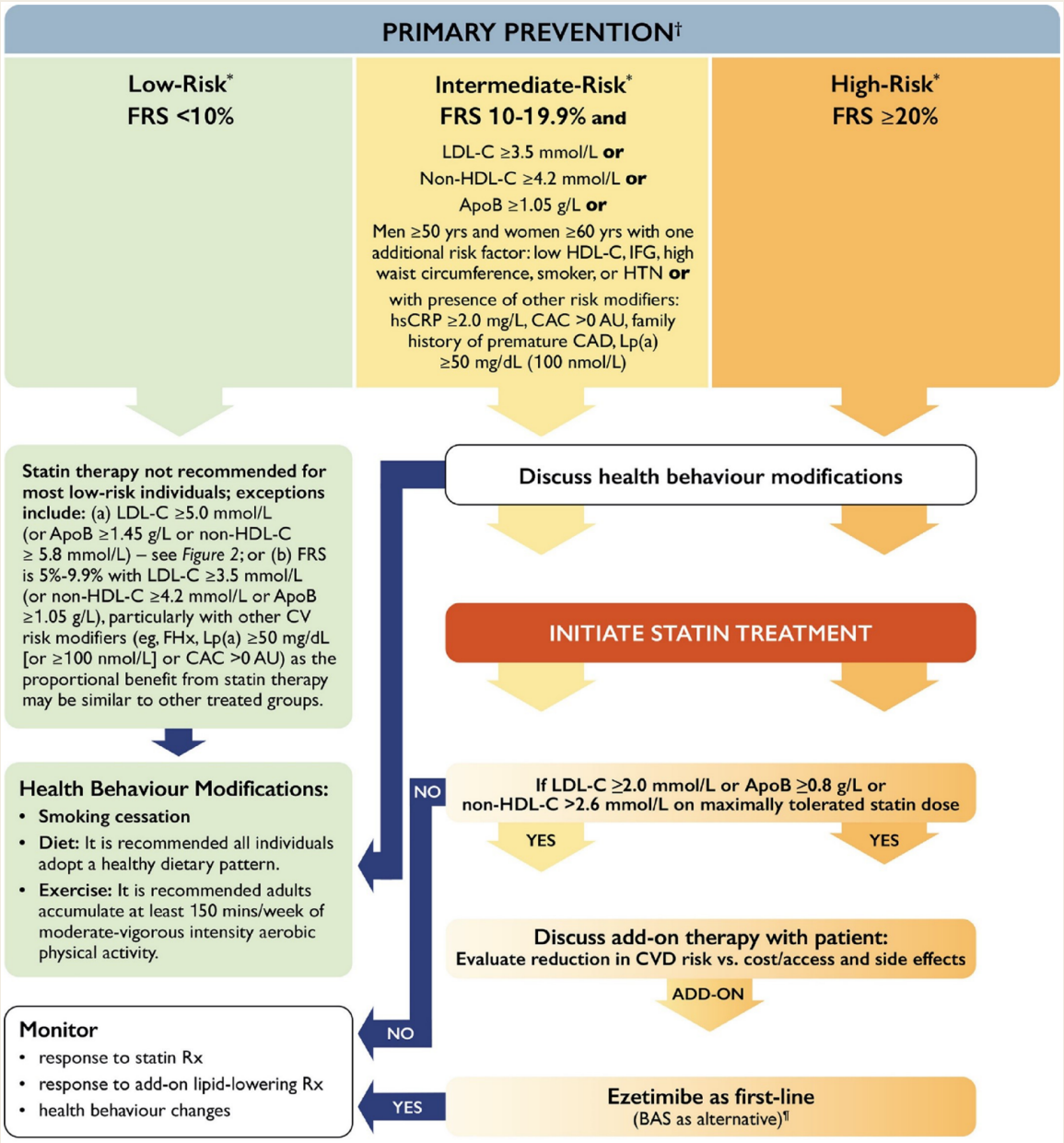
How should therapy be intensified?

Use thresholds (as opposed to targets) for therapy intensification

Once statin therapy is initiated, therapy is then intensified if a patient's follow-up lipid parameter remains above the defined threshold. This is a change from the previous approach that used a specific lipid target. There are several reasons why targets were changed to thresholds in the new guidelines. There is no robust randomized controlled trial evidence to support clear targets to which LDL-C, non–HDL-C, or ApoB levels should be lowered. Instead, trials have generally used thresholds of LDL-C (or non–HDL-C or ApoB) levels for initiation and intensification of therapy. Recent trials in secondary ASCVD prevention patients have used an LDL-C threshold of 1.8 mmol/L for intensification of therapy beyond statins, which is reflected in the algorithm of the new guidelines (Figure 2).[18,19] Lower concentrations of plasma LDL-C levels are associated with a lower risk of ASCVD events, which supports a causal relationship between LDL-C (as well as non–HDL-C and ApoB) and ASCVD.[18-25] Furthermore, recent evidence does not suggest that there are any risks associated with achieving very low LDL-C levels in trials with moderate duration of follow-up.[26,27]

1. Once patients are on a maximally tolerated statin dose, through shared decision-making with the patient, the new guidelines recommend titration of therapy based on the following thresholds:
   a. Statin-indicated conditions:
      i. In patients with a baseline LDL ≥5 mmol/L (or ApoB ≥1.45 g/L or non–HDL-C ≥5.8 mmol/)

FIGURE 1 Treatment approach for primary prevention patients



Statin indicated conditions consists of all documented ASCVD conditions, as well as other high-risk primary prevention conditions in the absence of ACSVD, such as most patients with diabetes, those with chronic kidney disease and those with a LDL-C ≥5.0 mmol/L.

†Calculate risk using the Framingham Risk Score (FRS) – refer to the iCCS available on the App Store or on Google Play

*Screening should be repeated every 5 years for men and women aged 40 to 75 years using the modified FRS or CLEM to guide therapy to reduce major CV events. A risk assessment might also be completed whenever a patient's expected risk status changes.

¶ studies have evaluated the efficacy of BAS for the prevention of ASCVD, but results have been inconclusive.

FRS = Framingham risk score; LDL-C = low-density lipoprotein cholesterol; HDL-C = high-density lipoprotein cholesterol; ApoB = apolipoprotein B; IFG = impaired fasting glucose; HTN = hypertension; hsCRP = high-sensitivity C-reactive protein; CAC = coronary artery calcium; AU – Agatston unit; Rx = prescription; BAS = bile acid sequestrant

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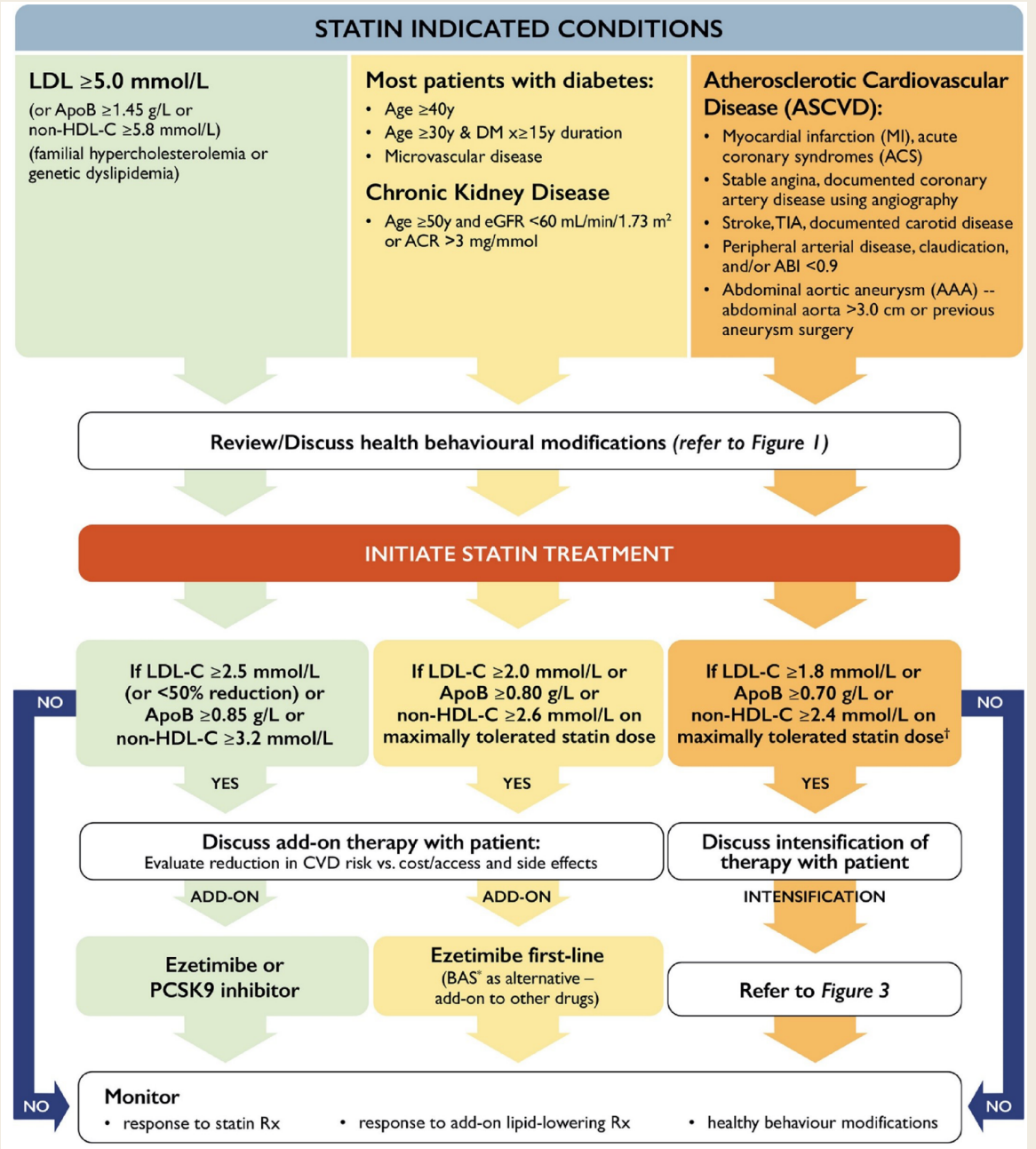
FIGURE 2 Treatment approach for statin-indicated patients



eGFR = estimated glomerular filtration rate; ACR = albumin-to-creatinine; TIA = transient ischemic attack; ABI = ankle-brachial index.
†LDL-C threshold selected on the basis of the PCSK9-inhibitor clinical trials lipid inclusion parameters with percentile equivalents used for ApoB and non-HDL-C.
*studies have evaluated the efficacy of BAS for the prevention of ASCVD, but results have been inconclusive.

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or documented familial hypercholesterolemia, consider therapy intensification with ezetimibe or a PCSK9 inhibitor if LDL-C ≥2.5 mmol/L (or <50% reduction), or ApoB ≥0.85 g/L, or non–HDL-C ≥3.2 mmol/L.

ii. In patients with diabetes mellitus or CKD, intensify therapy with ezetimibe (or bile acid sequestrants as an alternative) if LDL-C ≥2.0 mmol/L (or <50% reduction), or ApoB ≥0.80 g/L, or non–HDL-C ≥2.6 mmol/L.

iii. In patients with ASCVD, consider therapy intensification with ezetimibe and/or a PCSK9 inhibitor if LDL-C ≥1.8 mmol/L, or ApoB ≥0.7 g/L, or non–HDL-C ≥2.4 mmol/L (Figure 3), or

iv. In patients with ASCVD, consider therapy intensification with icosapent ethyl (IPE) if TG ≥1.5-5.6 mmol/L.

B. Primary prevention patients:

i. Intensify therapy with ezetimibe (or a bile acid sequestrant as an alternative) if LDL-C >2 mmol/L, or ApoB >0.8 g/L, or non–HDL-C >2.6 mmol/L.

Nonstatin therapy options

Since the 2016 CCS guidelines, new evidence has provided further clarity on the role of nonstatin therapy, as summarized in Table 3. Further details on the role of nonstatin therapy options are described below.

Ezetimibe. The 2021 CCS dyslipidemia guidelines continue to recommend ezetimibe as second-line therapy based on the results of the IMPROVE-IT trial, which was presented in the 2016 CCS guidelines.[33,34] Briefly, the IMPROVE-IT trial showed a modest reduction in a composite cardiovascular outcome when ezetimibe was added to statin therapy in patients with a recent ACS. Ezetimibe is recommended as potential add-on therapy to statins in both primary and secondary prevention patients. However, because ezetimibe reduces LDL-C by approximately 20% on top of statin therapy, it may be preferrable to start with a PCSK9 inhibitor as an add-on therapy if a patient has ASCVD and an LDL-C >2.2 mmol/L (or >20% above threshold).

PCSK9 inhibitors. Since the 2016 CCS dyslipidemia guidelines, 2 new trials (FOURIER and ODYSSEY OUTCOMES) with PCSK9 inhibitors have been published (refer to Table 3 for details).[18,19] Both evolocumab and alirocumab lower LDL-C by about 60% when used in addition to statin therapy and are approved for add-on therapy to statins in secondary ASCVD prevention patients and familial hypercholesterolemia patients. Cost may be a barrier to access to PCSK9 inhibitor therapy.

IPE. IPE is a prescription-only, highly purified formulation of ethyl eicosapentaenoic acid (EPA) that was recently approved for use in Canada on the basis of the REDUCE-IT trial (refer to Table 3 for details).[28] However, cost may be a barrier to access. Pharmacists should inform patients of the potential benefits, as well as the cost of IPE, to engage in a shared decision-making process when this therapy is indicated.

Omega-3 polyunsaturated fatty acids. While IPE has been shown to decrease cardiovascular events, it should not be inferred that the same benefit could be extrapolated to other omega-3 formulations, which include a combination of nonpurified EPA, docosahexaenoic acid, alpha linolenic acid, or other omega fatty acids (e.g., omega-6 or omega-9 fatty acids) from over-the-counter supplements or dietary sources. The guidelines do not recommend the use of these agents for CVD risk reduction.[29-32]

There are no new recommendations regarding the specific use of fibrates, bile acid sequestrants, or niacin since the 2016 CCS guidelines.

What lifestyle modifications are recommended?

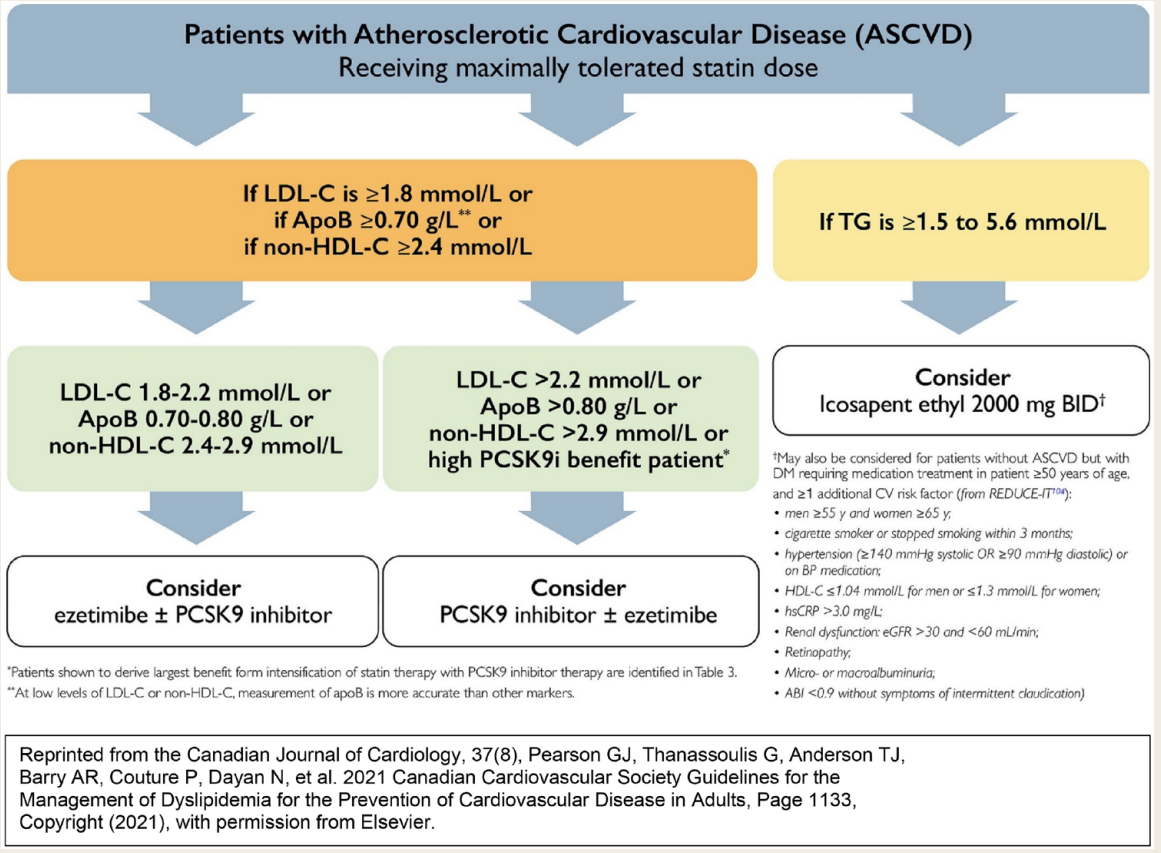
The 2021 CCS dyslipidemia guidelines continue to recommend health behaviour modifications as the cornerstone of CVD prevention in all patients.[6,35,36] Pharmacists can reinforce the following lifestyle modifications:

1. Tobacco: Counsel and assist with the cessation of tobacco use.
2. Alcohol: Educate patients on what is considered a safe amount of alcohol consumption, and encourage patients to adhere to these limits. In Canada's new guidance on alcohol and consumption report,[37] it is recognized that no amount of alcohol is good for your health, and drinking even a small amount has potential negative consequences. Importantly, it is identified that the risk for heart disease and stroke increases with consumption of 7 or more drinks per week.
3. Diet: Encourage all patients to maintain a healthy dietary pattern, such as the Mediterranean diet, avoiding trans fats and substituting polyunsaturated fats for saturated fats.
4. Activity: Encourage all patients to achieve 150 minutes of moderate to vigorous aerobic activity per week, in addition to adding muscle- and bone-strengthening activities at least 2 days per week. In secondary prevention patients, reducing sedentary behaviour can be additive to regular physical activity for reducing cardiovascular events.

Implementation tips for pharmacists

Clinical trial evidence has demonstrated the value of pharmacist screening for dyslipidemia and prescribing in improving control of dyslipidemia when added to usual medical care.[3,4]

FIGURE 3 Treatment intensification beyond statins for patients with atherosclerotic cardiovascular disease



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Consequently, pharmacists should practise to the full scope possible in their province to take an active role in the management of patients with dyslipidemia and at risk for cardiovascular disease.

- Identify and screen patients:
  - Some pharmacies provide point-of-care testing for lipid values depending on availability and provincial legislation.
  - Conduct cardiovascular risk assessment for patients identified in Table 2 (whom to screen for dyslipidemia) using the modified FRS or the Cardiovascular Life Expectancy Model.
  - Be aware of patients with a statin-indicated condition, as there is no need to conduct a cardiovascular risk assessment to guide treatment decisions since this group is treated based on clinical conditions (Figure 2).
  - Where authorized, order appropriate laboratory assessments as outlined in Table 2 (what to screen for dyslipidemia).
- Ensure that all patients are treated appropriately:
  - Emphasize the importance of health behaviour modifications for all patients at risk of cardiovascular disease.
  - Recognize patients who would benefit from initiation of a statin:
    - Those with a statin-indicated condition
    - High-risk primary prevention patients (modified FRS ≥20%)
    - Intermediate-risk primary prevention patients (modified FRS 10%-19.9%) and an LDL-C ≥3.5 mmol/L (or non–HDL-C ≥4.2 mmol/L or ApoB ≥1.05 g/L)
  - Ensure that patients who are eligible for statin therapy are receiving a high-intensity or maximally tolerated dose.
  - Monitor response to statin therapy and determine patients who may be appropriate for intensification of lipid-lowering therapy (addition of ezetimibe and/or a PCSK9 inhibitor) based on the recommended lipid thresholds (Figure 2) and facilitate medication access, where appropriate.
  - Identify patients who may benefit from the addition of IPE, such as those with ASCVD who are receiving a maximally tolerated statin dose, with TG ≥1.5 to 5.6 mmol/L (refer to Figure 3, for all eligible patients) and facilitate medication access, where appropriate.
  - Do not recommend over-the-counter omega-3 fatty acids for cardiovascular risk reduction, and educate

TABLE 3 Summary of key new therapy evidence

PCSK9 inhibitors	The FOURIER trial randomized 27,564 patients with ASCVD and ≥1 cardiovascular risk factors and LDL-C ≥1.8 mmol/L on maximally tolerated statin therapy to evolocumab (140 mg subcutaneously every 2 weeks or 420 mg subcutaneously every 4 weeks) or placebo.[18] At a median follow-up of 2.2 years, evolocumab reduced composite cardiovascular outcomes (NNT of 67), which was primarily driven by a reduction in nonfatal MI. There was no significant reduction in cardiovascular and all-cause death. The most common adverse effects were injection-site reactions. The ODYSSEY OUTCOME trial randomized 18,924 patients with an ACS within 1-12 months and LDL-C ≥1.8 mmol/L on maximally tolerated statin therapy to alirocumab (75 mg subcutaneously every 2 weeks, dose adjusted to an LDL-C of 0.65-1.3 mmol/L) or placebo.[19] At a median follow-up of 2.8 years, alirocumab reduced the composite cardiovascular outcomes (NNT of 63), which was primarily driven by a reduction in nonfatal MI and ischemic stroke. There was no significant difference in the rates of all-cause death or cardiovascular death. The most common adverse effects were injection-site reactions.
IPE	The REDUCE IT trial randomized 8179 patients with ASCVD or patients with diabetes and ≥1 cardiovascular risk factor with a TG level of 1.5-5.6 mmol/L on statin therapy to IPE 2000 mg orally twice daily or mineral oil as placebo. At a median follow-up of 4.9 years, IPE reduced the composite cardiovascular outcome (NNT of 21), in addition to cardiovascular death (NNT of 112).[28] There was no significant difference in all-cause death. At 1 year, triglyceride levels were modestly reduced from baseline by about 18%. While serious bleeding was not significantly different between the groups, atrial fibrillation (NNH of 72) and peripheral edema (NNH of 67) were significantly higher with IPE.
PUFAs	The ASCEND trial randomized 15,480 patients who were ≥40 years of age with diabetes but without CVD to PUFAs (1000 mg orally once daily) or placebo.[29] After a mean follow-up of 7.4 years, there was no significant difference in composite or individual cardiovascular outcomes. The VITAL trial randomized 25,871 primary prevention patients (men who were ≥50 years of age and women who were ≥55 years of age) to n-3 PUFAs (1000 mg orally once daily) or placebo.[30] At a median follow-up of 5.3 years, there was no significant difference in the composite cardiovascular outcome. The STRENGTH trial randomized 13,078 patients at high risk of CVD on statin therapy to a pharmaceutical carboxylic acid formulation of EPA and DHA at a dose of 4000 mg orally per day or corn oil as placebo.[31] The study was discontinued prematurely after a median follow-up of 3.5 years by the data safety monitoring board due to futility, as there was no significant reduction in cardiovascular outcomes. Gastrointestinal adverse effects were more common in the active treatment group. A 2018 meta-analysis of 79 randomized controlled trials (112,059 patients) that investigated fish and plant-based omega-3 PUFA supplementation for at least 12 months did not find a significant reduction in cardiovascular outcomes or mortality compared with placebo.[32]

ACS, acute coronary syndrome; ASCVC, atherosclerotic cardiovascular disease; DHA, docosahexaenoic acid; EPA, eicosapentaenoic acid; IPE, icosapent ethyl; LDL-C, low-density lipoprotein cholesterol; MI, myocardial infarction; NNH, number needed to harm; NNT, number needed to treat; PUFAs, omega-3 (or n-3) polyunsaturated fatty acids; TG, triglycerides.

patients who are self-selecting these products about the recent evidence demonstrating a lack of benefit.
- Ensure that patients are educated about the risks and benefits of any lipid-lowering therapy they are prescribed.

Conclusion

The 2021 CCS dyslipidemia guidelines are relevant to pharmacists who provide care to patients with dyslipidemia and who are at risk for cardiovascular disease. This article summarizes the updated dyslipidemia guidelines for pharmacists, but readers are encouraged to refer to the full guidelines for additional details.[6] In addition, pharmacists can access several useful practice tools and education resources for the management of dyslipidemia on the CCS website (https://www.ccs.ca/en/guidelines/guideline-resources). ■

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References

1. Statistics Canada. *Leading causes of death, total population, by age group*. 2022. Available: https://www150.statcan.gc.ca/t1/tbl1/en/tv.action?pid=1310039401 (accessed Feb. 20, 2022).
2. Public Health Agency of Canada. *Report from the Canadian Chronic Disease Surveillance System: heart disease in Canada, 2018*. 2018. Available: https://www.canada.ca/content/dam/phac-aspc/documents/services/publications/diseases-conditions/report-heart-disease-canada-2018/pub1-eng.pdf (accessed Feb. 20, 2022).
3. Tsuyuki RT, Rosenthal M, Pearson GJ. A randomized trial of a community-based approach to dyslipidemia management: pharmacist prescribing to achieve cholesterol targets (RxACT study). *Can Pharm J (Ott)* 2016;149:283-92.
4. Tsuyuki RT, Al Hamarneh YN, Jones CA, Hemmelgarn BR. The effectiveness of pharmacist interventions on cardiovascular risk: the multicenter randomized controlled RxEACH trial. *J Am Coll Cardiol* 2016;67:2846-54.
5. Charrois TL, Zolezzi M, Koshman SL, et al. A systematic review of the evidence for pharmacist care of patients with dyslipidemia. *Pharmacotherapy* 2012;32(3):222-33.
6. Pearson GJ, Thanassoulis G, Anderson TJ, et al. 2021 Canadian Cardiovascular Society guidelines for the management of dyslipidemia for the prevention of cardiovascular disease in adults. *Can J Cardiol* 2021;37(8):1129-50.
7. Bellamy L, Casas JP, Hingorani AD, Williams DJ. Pre-eclampsia and risk of cardiovascular disease and cancer in later life: systematic review and meta-analysis. *BMJ* 2007;335:974.
8. Grandi SM, Filion KB, Yoon S, et al. Cardiovascular disease-related morbidity and mortality in women with a history of pregnancy complications. *Circulation* 2019;139:1069-79.
9. Clarke R, Peden JF, Hopewell JC, et al. Genetic variants associated with Lp(a) lipoprotein level and coronary disease. *N Engl J Med* 2009;361:2518-28.
10. Kamstrup PR, Tybjaerg-Hansen A, Steffensen R, Nordestgaard BG. Genetically elevated lipoprotein(a) and increased risk of myocardial infarction. *JAMA* 2009;301:2331-9.
11. Emerging Risk Factors Collaboration, Erqou S, Kaptoge S, et al. Lipoprotein(a) concentration and the risk of coronary heart disease, stroke and nonvascular mortality. *JAMA* 2009;302:412-23.
12. Madsen CM, Kamstrup PR, Langsted A, Varbo A, Nordestgaard BG. Lipoprotein(a)-lowering by 50 mg/dL (105 nmol/L) may be needed to reduce cardiovascular disease 20% in secondary prevention: a population-based study. *Arterioscler Thromb Vasc Biol* 2020;40:255-66.
13. Sniderman AD, Williams K, Contois JH, et al. A meta-analysis of low-density lipoprotein cholesterol, non-high-density lipoprotein cholesterol and apolipoprotein B as markers of cardiovascular risk. *Circ Cardiovasc Qual Outcomes* 2011;4(3):337-45.
14. Boekholdt SM, Arsenault BJ, Mora S, et al. Association of LDL cholesterol, non-HDL cholesterol and apolipoprotein B levels with risk of cardiovascular events among patients treated with statins: a meta-analysis. *JAMA* 2012;307(12):1302-9.
15. Yusuf S, Bosch J, Dagenais G, et al. Cholesterol lowering in intermediate-risk persons without cardiovascular disease. *N Engl J Med* 2016;374:2021-31.
16. Gencer B, Marston NA, Im K, et al. Efficacy and safety of lowering LDL cholesterol in older patients: a systematic review and meta-analysis of randomised controlled trials. *Lancet* 2020;396:1637-43.
17. Thanassoulis G, Williams K, Altobelli KK, et al. Individualized statin benefit for determining statin eligibility in the primary prevention of cardiovascular disease. *Circulation* 2016;133:1574-81.
18. Sabatine MS, Giugliano RP, Keech AC, et al. Evolocumab and clinical outcomes in patients with cardiovascular disease. *N Engl J Med* 2017;376(18):1713-22.
19. Schwartz GG, Steg PG, Szarek M, et al. Alirocumab and cardiovascular outcomes after acute coronary syndrome. *N Engl J Med* 2018;379(22):2097-07.
20. Silverman MG, Ference BA, Im K, et al. Association between lowering LDL-C and cardiovascular risk reduction among different therapeutic interventions: a systematic review and meta-analysis. *JAMA* 2016:312(12):1289-97.
21. Raal FJ, Honarpour N, Blom DJ, et al. Inhibition of PCSK9 with evolocumab in homozygous familial hypercholesterolaemia (TESLA Part B): a randomised, double- blind, placebo-controlled trial. *Lancet* 2015;385:341-50.
22. Ference BA, Ginsberg HN, Graham I, et al. Low-density lipoproteins cause atherosclerotic cardiovascular disease. 1. Evidence from genetic, epidemiologic, and clinical studies. A consensus statement from the European Atherosclerosis Society Consensus Panel. *Eur Heart J* 2017;38:2459-72.
23. Borén J, Chapman MJ, Krauss RM, et al. Low-density lipoproteins cause atherosclerotic cardiovascular disease: pathophysiological, genetic, and therapeutic insights: a consensus statement from the European Atherosclerosis Society Consensus Panel. *Eur Heart J* 2020;41(24):2313-30.
24. Grundy SM, Stone NJ, Bailey AL, et al. 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA guideline on the management of blood cholesterol: a report of the American College of Cardiology/

American Heart Association task force on clinical practice guidelines. *Circulation* 2019;139(25):e1082-1143.

25. Cholesterol Treatment Trialists' (CTT) Collaborators, Mihaylova B, Emberson J, et al. The effects of lowering LDL cholesterol with statin therapy in people at low risk of vascular disease: meta-analysis of individual data from 27 randomised trials. *Lancet* 2012;11;380(9841):581-90.

26. HPS3/TIMI55–REVEAL Collaborative Group, Bowman L, Hopewell JC, et al. Effects of anacetrapib in patients with atherosclerotic vascular disease. *N Engl J Med* 2017;377:1217-27.

27. Giugliano RP, Peterson TR, Park G, et al. Clinical efficacy and safety of achieving very low LDL-cholesterol concentrations with the PCSK9 inhibitor evolocumab: a prespecified secondary analysis of the further cardiovascular outcomes research with PCSK9 inhibition in subjects with elevated risk (FOURIER) trial. *Lancet* 2017;390:1962-71.

28. Bhatt DL, Steg PG, Miller M, et al. Cardiovascular risk reduction with icosapent ethyl for hypertriglyceridemia. *N Engl J Med* 2019;380:11-22.

29. ASCEND Study Collaborative Group, Bowman L, Mafham M, et al. Effects of n-3 fatty acid supplements in diabetes mellitus. *N Engl J Med* 2018;9:1540-50.

30. Manson JE, Cook NR, Lee IM, et al. Marine n-3 fatty acids and prevention of cardiovascular disease and cancer. *N Engl J Med* 2019;380:23-32.

31. Nicholls SJ, Lincoff AM, Garcia M, et al. Effect of high-dose omega-3 fatty acids vs corn oil on major adverse cardiovascular events in patients at high cardiovascular risk: the STRENGTH randomized clinical trial. *JAMA* 2020;324:2268-80.

32. Abdelhamid AS, Brown TJ, Brainard JS, et al. Omega-3 fatty acids for the primary and secondary prevention of cardiovascular disease. *Cochrane Database Syst Rev* 2018;11:CD003177.

33. Robinson JG, Rosenson RS, Farnier M, et al. Safety of very low low-density lipoprotein cholesterol levels with alirocumab: pooled data from randomized trials. *J Am Coll Cardiol* 2017;69:471-82.

34. Cannon CP, Blazing MA, Giugliano RP, et al. Ezetimibe added to statin therapy after acute coronary syndromes. *N Engl J Med* 2015;372:2387-97.

35. Anderson TJ, Gregoire J, Pearson GJ, et al. 2016 Canadian Cardiovascular Society guidelines for the management of dyslipidemia for the prevention of cardiovascular disease in the adult. *Can J Cardiol* 2016;32:1263-82.

36. Yusuf S, Hawken S, Ounpuu S, et al. Effect of potentially modifiable risk factors associated with myocardial infarction in 52 countries (the INTERHEART study): case-control study. *Lancet* 2004;364:937-52.

37. Paradis C, Butt P, Shield K, et al., Low-Risk Alcohol Drinking Guidelines Scientific Expert Panels. *Canada's guidance on alcohol and health: final report*. 2023. Ottawa (ON): Canadian Centre on Substance Use and Addiction. Available: https://ccsa.ca/canadas-guidance-alcohol-and-health (accessed Feb. 27, 2023).